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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/587,386	05/03/2007	Stefan Schorling	22398-US	4893

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Roche Molecular Systems, Inc.
Patent Law Department
4300 Hacienda Drive
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EXAMINER	
BAUGHMAN, MOLLY E	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/587,386	SCHORLING, STEFAN	
	Examiner	Art Unit	
	Molly E. Baughman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☒ Claim(s) *1-16* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/5/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-17, and election of SEQ ID NO:11, 15, and 17, in the reply filed on 11/17/08 is acknowledged.

2. Claims 18-24 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/17/08.

3. Applicant's cancellation of claims 17-24 in the reply filed on 11/17/08 is acknowledged.

Election/Restrictions

4. Upon further consideration, the examiner has determined that an election of an additional sequence (an additional probe sequence) is applicable for prosecution of the claims. In a telephone conversation with Robert Mann on 1/27/09 a provisional election was made of SEQ ID NO:10, thereby resulting in the final election of sequences to be SEQ ID NO:10, 11, 15 and 17 for prosecution on the merits. Affirmation of this election must be made by applicant in replying to this Office action.

5. Claims 1-16 and corresponding SEQ ID NO: 10, 11, 15 and 17 are currently under examination.

Information Disclosure Statement

6. The information disclosure statement (IDS) submitted on 9/5/06 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, some citations have been either modified, or lined through for the following reasons:

a. The International Search and Examination Report (citation 19) has been fully considered, although, it have been lined through as it is not an appropriate document for printed patents.

b. Citations 22, 23, and 25 have been lined and not considered as they are in a foreign language and translation must be submitted for consideration.

c. Citation 42 has been considered only for the submitted English *abstract*, as the original document is in a foreign language.

Claim Objections

7. Claims 1-16 are objected to because of the following informalities: The claims contain non-elected subject matter and do not reflect the elected sequences. For instance, claim 1 still states that the "first primer consists of at least contiguous 12 nucleotides of a nucleic acid sequence selected from the nucleic acid sequence SEQ ID NO:2." For purposes of examination, the claims will be examined as though the primers are SEQ ID NO:15 and 17 and the probe sequences are SEQ ID NO:11 and 10, where appropriate. Additionally, the claims which are drawn to limitations of different primers, and therefore are not further limiting (i.e. claim 2 and 3), will be included in the rejections based on the independent claims. Appropriate correction is required.

Claim Rejections - 35 USC § 112

8. Claims 7 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 7 recites the limitation "said hybridizing step d)" in claim 6 (and ultimately in claim 4). There is insufficient antecedent basis for this limitation in the claim.

b. Claim 10 recites the limitation "the first or second fluorescent label" in claim 9 (and ultimately in claim 4). There is insufficient antecedent basis for this limitation in the claim.

Claim Interpretation

9. As noted above in the claim objections, the claims contain non-elected subject matter. Therefore, in order to expedite prosecution, the claims will be examined as though the first primer *has the nucleic acid sequence SEQ ID NO:15* and the second primer *has the nucleic acid sequence SEQ ID NO:17*. Such language is consistent with the language presented in claim 3, which comprises the sequences. Claim 1-3 will be examined only for such sequences, as required by the restriction requirement. Likewise, claims 4, 13 and 14 will be interpreted in such a manner as well. Additionally, claims presenting the elected probe sequences of SEQ ID NO:10 and 11 will be examined for their sequences alone, as represented by the claim language in claim 12.

For instance, in claim 11, the claim will be interpreted as "where the probe has the nucleic acid sequence SEQ ID NO:10 or a complementary sequences thereof." Such an interpretation is consistent with the restriction requirement.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Manaresi et al., "Diagnosis and Quantitative Evaluation of Parvovirus B19 Infections by Real-Time PCR in the Clinical Laboratory," J. Medical Virology, 2002, Vol.67, pp.275-281, in view of Hemauer et al., "Sequence variability among different parvovirus B19 isolates," J. General Virology, 1996, Vol.77, pp.1781-1785 (of record).

Regarding claims 1-3, Manaresi discuss a method comprising (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid, and (d) detecting the amplified target nucleic acid of step (c) (see abstract and pg.277, "Real-Time B19 PCR," left column).

Manaresi does not discuss the method whereby the first primer has a nucleic acid sequence SEQ ID NO:15, and whereby the second primer has a nucleic acid sequence SEQ ID NO:17.

Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO:15 (nucleotides 121-140) and 17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the NS1 coding region, and is more specifically included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

One of ordinary skill in the art would have been motivated to modify the method of Manaresi to use primers of SEQ ID NO:15 and 17 because Hemauer et al. shows that the Parvovirus B19 sequence comprising these primer sequences was known in the art and designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO:15 and 17 are located in this conserved stretch, one of skill would have recognized that amplification of such a conserved region would allow for amplification of multiple different parvovirus B19 sequences in a universal detection method. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Manaresi to use primers derived from the well-known and amplifiable conserved stretch of the NSC-1 region, resulting in amplification and detection of multiple different parvovirus sequence variants. It would have been

obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed primer sequences therein.

12. Claims 1-5, and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schmidt et al., "Parvovirus B19 DNA in plasma pools and plasma derivatives," Vox Sanguinis, 2001, Vol.81, No.4, pp.228-235 (of record), in view of Hemauer et al., "Sequence variability among different parvovirus B19 isolates," J. General Virology, 1996, Vol.77, pp.1781-1785 (of record), and further in view of Buck et al., "Design Strategies and Performance of Custom DNA Sequencing Primers," Biotechniques, Sept. 1999, Vol.27, No.3, pp. 528-536.

Regarding claims 1-3, Schmidt discuss a method comprising (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid, and (d) detecting the amplified target nucleic acid of step (c) (see pg.229, "Quantitative TaqMan PCR" where Schmidt discusses the method including two primers and a doubly labeled probe within the NS1 region. Schmidts states the primers and probes are within nucleotides 2030 to 2171 of the B19 Genome).

Schmidt does not discuss the method whereby the first primer has a nucleic acid sequence SEQ ID NO:15, and whereby the second primer has a nucleic acid sequence SEQ ID NO:17, however, his primers are nearby as SEQ ID NO:15 and 17 are located within the same NS1 region of the Parvovirus B19 genome.

Regarding claims 4-5, 8, and 10-14, Schmidt discusses a method comprising: (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of

primers comprising a first and a second primer, (c) amplifying the target nucleic acid, (d) contacting the sample with a probe under conditions for binding the probe to the target nucleic acid, and (e) detecting the binding product between the target nucleic acid and the probe as an indication of the presence of the target nucleic acid (see pg.229, "Quantitative TaqMan PCR" where Schmidt discusses the method including two primers and a doubly labeled probe within the NS1 region. Schmidts states the primers and probes are within nucleotides 2030 to 2171 of the B19 Genome).

Regarding claim 9, Schmidt discusses the method wherein the target nucleic acid in step c) is amplified with a template-dependent DNA polymerase (see pg.229, "Quantitative TaqMan PCR" where Schmidt uses TaqGold Polymerase).

Schmidt does not discuss the method whereby the first primer has a nucleic acid sequence SEQ ID NO:15, and whereby the second primer has a nucleic acid sequence SEQ ID NO:17 [i.e. claims 4, and 13-14], nor wherein the probe has the sequence of SEQ ID NO:10 or 11 [i.e. claims 11-12], however, his primers and probe are nearby to such sequences as the instant SEQ ID NO:10, 11, 15 and 17 are located within the same NS1 region of the Parvovirus B19 genome.

Additionally, Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO:10 (nucleotides 147-183), SEQ ID NO:11 (nucleotides 147-172), SEQ ID NO:15 (nucleotides 121-140) and SEQ I D NO:17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the

NS1 coding region, and is more specifically included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

In the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers and probe simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for detection of the NS1 region of the Parvovirus B19 genome and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of a polynucleotide sequence, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is

not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to modify the method of Schmidt to use primers of SEQ ID NO:15 and 17 and a probe sequence of SEQ ID

NO:10 or 11 because Schmidt demonstrates the benefits of designing and using similar primers and a probe targeting the NS1 region of the Parvovirus B19 genome, and Hemauer et al. shows that the Parvovirus B19 sequence comprising the primer sequences of SEQ ID NO:15 and 17 and probe sequences of SEQ ID NO:10 and 11 was known in the art and also designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO:15 and 17, and probe sequences of SEQ ID NO:10 and 11 are located in this conserved stretch, one of skill would have recognized that amplification and detection of such a conserved region would allow for detection of multiple different parvovirus B19 sequences in a universal method. Furthermore, Buck et al. demonstrate the capability of multiple primers to equivalently amplify the same targeted region. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Schmidt to substitute for similar and equivalent primers and a probe derived from the same well-known and amplifiable conserved stretch of the NSC-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. It would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed primer and probe therein.

13. Claims 1-7, 9, and 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harder et al., "New LightCycler PCR for Rapid and Sensitive Quantification of Parvovirus B19 DNA Guides Therapeutic Decision-Making in Relapsing Infections," J. Clin.Microbiol., 2001, Vol.39, No.12, pp.4413-4419 (of record), in view of Hemauer et al., "Sequence variability among different parvovirus B19 isolates," J. General Virology, 1996, Vol.77, pp.1781-1785 (of record), and further in view of Buck et al., "Design Strategies and Performance of Custom DNA Sequencing Primers," Biotechniques, Sept. 1999, Vol.27, No.3, pp. 528-536.

Regarding claims 1-3, Harder et al. discuss a method comprising (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid, and (d) detecting the amplified target nucleic acid of step (c) (see pg.4414, "LC-depedent amplification of B19 DNA" where Harder uses NS-1a and NS-1a' as primers and two adjacent donor/acceptor probes in a real-time SYBR green PCR assay).

Harder does not discuss the method whereby the first primer has a nucleic acid sequence SEQ ID NO:15, and whereby the second primer has a nucleic acid sequence SEQ ID NO:17, however, his primers are nearby as SEQ ID NO:15 and 17 are located within the NS1 region of the Parvovirus B19 genome.

Regarding claims 4-7, and 10-14, Harder discusses a method comprising: (a) providing a sample suspected to contain the target nucleic acid, (b) providing a pair of primers comprising a first and a second primer, (c) amplifying the target nucleic acid by

contacting the sample with the said pair of primers to produce an amplification product if the target nucleic acid is present in said sample, (d) contacting said sample with the pair of probes, wherein the members of said pair of probes hybridize to said amplification product within no more than five nucleotides of each other, wherein the first probe of said pair of probes is labeled with a donor fluorescent label and wherein the second probe of said pair of probes is labeled with a corresponding acceptor fluorescent label; and (e) detecting the presence or absence of fluorescence resonance energy transfer between said donor fluorescent label of said first probe and said acceptor fluorescent label of said second probe, wherein the presence of fluorescence resonance energy transfer is indicative of the presence of the target nucleic acid in the sample, and wherein the absence of fluorescence resonance energy transfer is indicative of the absence of the target nucleic acid in the sample (see pg.4414, "LC-depedent amplification of B19 DNA" where Harder uses NS-1a and NS-1a' as primers and two adjacent donor/acceptor probes in a real-time SYBR green PCR assay; and Figures 1 and 2).

Regarding claim 9, Harder discusses the method where amplification is performed using the FastStart SYBR green kit from Roche, which uses a FastStart Taq DNA polymerase that is a modified form of thermostable recombinant Taq DNA polymerase (Taq is a template-dependent DNA polymerase) (see pg.4414, "LC-dependent amplification of B19 DNA").

Harder does not discuss the method whereby the first primer has a nucleic acid sequence SEQ ID NO:15, and whereby the second primer has a nucleic acid sequence

SEQ ID NO:17 [i.e. claims 4, and 13-14], nor wherein the probe has the sequence of SEQ ID NO:10 or 11 [i.e. claims 11-12], however, his primers and probes are nearby to such sequences as the instant SEQ ID NO:10, 11, 15 and 17 are located within the NS1 region of the Parvovirus B19 genome.

Additionally, Hemauer teaches the Parvovirus B19 DNA, genome position 1924-2317, identified as Genbank Accession Number Z70553. This sequence comprises SEQ ID NO:10 (nucleotides 147-183), SEQ ID NO:11 (nucleotides 147-172), SEQ ID NO:15 (nucleotides 121-140) and SEQ I D NO:17 (nucleotides 270-251). In Hemauer's research, he identifies this region (i.e. genome position 1924-2317) being within the NS1 coding region, and is more specifically included in the NS1-C region (see Figure 1). Hemauer also teaches nearby primers to amplify this region (see Table 2 on pg.1783).

In the court decision *In Re Deuel* 34 USPQ 2d 1210 (Fed. Cir. 1995), the Court of Appeals for the Federal Circuit determined that the existence of a general method of identifying a specific DNA does not make the specific DNA obvious. Regarding structural or functional homologs, however, the Court stated,

"Normally, a *prima facie* case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound. Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties."

Since the claimed primers and probe simply represent structural homologs, which are derived from sequences suggested by the prior art as useful for detection of the NS1 region of the Parvovirus B19 genome and concerning which a biochemist of

ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of a polynucleotide sequence, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents, Buck expressly provides evidence of the equivalence of primers. Specifically, Buck invited primer submissions from a number of labs (39) (page 532, column 3), with 69 different primers being submitted (see page 530, column 1). Buck also tested 95 primers spaced at 3 nucleotide intervals along the entire sequence at issue, thereby testing more than 1/3 of all possible 18 mer primers on the 300 base pair sequence (see page 530, column 1). When Buck tested each of the primers selected by the methods of the different labs, Buck found that EVERY SINGLE PRIMER worked (see page 533, column 1). Only one primer ever failed, No. 8, and that primer functioned when repeated. Further, EVERY SINGLE CONTROL PRIMER functioned as well (see page 533, column 1). Buck expressly states "The results of the empirical

sequencing analysis were surprising in that nearly all of the primers yielded data of extremely high quality (page 535, column 2)." Therefore, Buck provides direct evidence that all primers would be expected to function, and in particular, all primers selected according to the ordinary criteria, however different, used by 39 different laboratories. It is particularly striking that all 95 control primers functioned, which represent 1/3 of all possible primers in the target region. This clearly shows that every primer would have a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to modify the method of Harder to use primers of SEQ ID NO:15 and 17 and a probe sequence of SEQ ID NO:10 or 11 because Harder demonstrates the benefits of designing and using similar primers and probes targeting the NS1 region of the Parvovirus B19 genome, and Hemauer et al. shows that the Parvovirus B19 sequence comprising the primer sequences of SEQ ID NO:15 and 17 and probe sequences of SEQ ID NO:10 and 11 was known in the art and also designed nearby primers that amplify this same region. Additionally, Hemauer also notes that amplification of the NSC-1 region was able to show positive PCR results in contrast to other regions of the Parvovirus B19 genome and also noted that there is a relatively conserved stretch of about 220 bp with only a few alterations in nucleotides 2020-2240 of this region (see pg.1783, right column). Therefore, since the sequences of primers SEQ ID NO:15 and 17, and probe sequences of SEQ ID NO:10 and 11 are located in this conserved stretch, one of skill would have recognized that amplification and detection of such a conserved region would allow for detection of multiple different parvovirus B19 sequences in a universal

method. Furthermore, Buck et al. demonstrate the capability of multiple primers to equivalently amplify the same targeted region. Therefore, the skilled artisan would have had a reasonable expectation of success in modifying the method of Harder to substitute for similar and equivalent primers and probes derived from the same well-known and amplifiable conserved stretch of the NSC-1 region, resulting in the predictable amplification and detection of multiple different parvovirus sequence variants. It would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods and use the claimed primer and probe sequences therein.

14. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schmidt et al. (2001), in view of Hemauer et al. (1996), and Buck et al. (1999), as applied to claims 1-5, and 8-14 above, OR Harder et al. (2001), in view of Hemauer et al. (1996), and Buck et al. (1999), as applied to claims 1-7, 9, and 10-14 above and further in view of Andrus et al. (US 7,348,164).

The teachings of the primary references are discussed above. These references do not discuss the method wherein the primer and/ or the probe comprise a modified nucleotide or a non-nucleotide compound.

However, Andrus demonstrates that the use of modified nucleotides or non-nucleotide compounds in primers and probes which detect Parvovirus B19 sequences was conventional in the art at the time of the invention (see abstract, Figures, and col.9, lines 59-67). Therefore, one of skill in the art would have had a reasonable expectation

of success in modifying the primer and/or probe of Schmidt, as modified by Hemauer and Buck, or Harder, as modified by Hemauer and Buck, to include a modified nucleotide or a non-nucleotide compound since Andrus demonstrates it was conventional to do in the art at the time of the invention. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and use the claimed primers and/or probe comprising modified nucleotides or a non-nucleotide compounds therein.

15. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Schmidt et al. (2001), in view of Hemauer et al. (1996), and Buck et al. (1999), as applied to claims 1-5, and 8-14 above, OR Harder et al. (2001), in view of Hemauer et al. (1996), and Buck et al. (1999), as applied to claims 1-7, 9, and 10-14 above, and further in view of Mosquera et al., "Simultaneous Detection of Measles Virus, Rubella Virus, and Parvovirus B19 by Using Multiplex PCR," J. Clin. Micro., 2002, Vol.40, No.1, pp.111-116.

The teachings of the primary references are discussed above. These references do not discuss the method wherein other target nucleic acids are detected in the same reaction.

However, it was conventional in the art to conduct multiplex PCR assays where Parvovirus B19 is detected within the multiplex, as demonstrated by Mosquera et al. Mosquera explains that it is beneficial to detect all three together as the rash illness caused by Rubella Virus, and Parvovirus B19 is easily confused with measles virus

infection and differential diagnosis is recommended for surveillance activities (see abstract and pg.11, right column, first full paragraph). Therefore, one of skill in the art would have had a reasonable expectation of success in modifying the method of either one of Schmidt, as modified by Hemauer and Buck, or Harder, as modified by Hemauer and Buck, to detect multiple target nucleic acids with Parvovirus B19 since Mosquera demonstrates that it was conventional in the art to conduct multiplex assays including Parvovirus B19 for the added benefit of being able to distinguish between viral infections which cause similar physical symptoms. It would have been *prima facie* obvious to one of skill in the art to carry out the claimed methods and also detect other target nucleic acids therein.

Summary

16. No claims are free of the prior art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Molly E. Baughman whose telephone number is (571)272-4434. The examiner can normally be reached on Monday-Friday 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637

/Molly E Baughman/
Examiner, Art Unit 1637